FORM PTO-1390 (REV. 11-2000) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: Z70538-1P US

U.S. APPLICATION NO (If known, see 37 CFR 1.5): 10/009574

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB00/01875	May 16, 2000	May 19, 1999

TITLE OF INVENTION: Method of Treatment

APPLICANT(S) FOR DO/EO/US: AstraZeneca AB

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. [ ] The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is attached hereto (required only if not communicated by the International Bureau).
   b. [X] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. [ ] is attached hereto.
   b. [ ] has been previously submitted under 35 U.S.C. 154(d)(4).
7. [ ] Amendments to the claims of the International Aplication under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] An English lanugage translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
14. [ ] A SECOND or SUBSEQUENT preliminary amendment.
15. [ ] A substitute specification.
16. [ ] A change of power of attorney and/or address letter.
17. [ ] A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. [ ] A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. [ ] A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. [ ] Other items or information:

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
10/009574		

21. ☐ The following fees are submitted:	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	12 - 20 =		x **$18.00**	$	
Independent claims	4 - 3 =	1	x **$80.00**	$ 80.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$270.00**	$	
TOTAL OF ABOVE CALCULATIONS =				$	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2. +				$	
SUBTOTAL =				$	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
TOTAL NATIONAL FEE =				$	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				$ 940.00	
				Amount to be refunded:	$
				charged:	$

a. ☐ A check in the amount of $ _____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 26-0166 in the amount of $ 940.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 26-0166 . A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Customer No. 22466
AstraZeneca Pharmaceuticals
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K F Mitchell
SIGNATURE

Kenneth F. Mitchell
NAME

42,007
REGISTRATION NUMBER

Docket No. Z70538-1P US

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Application of: **Reinstein , *et al.***
Application No: **National filing of PCT/GB00/01875**
For: **Method of Treatment**

Group Art Unit: Not Allocated
Examiner: Not Allocated

Assistant Commissioner for Patents
Box Patent Application
Washington, DC 20231

Preliminary Amendment

Sir:

This preliminary Amendment accompanies a filing of a National Stage Application under 35 U.S.C. § 371 of International Application No. PCT/GB00/01875 the priority of which is hereby claimed.

AMENDMENT

In the Claims:

Please **CANCEL** original claims 3, 4, 7 and 8 without prejudice, and enter the following amended claims 3, 4, 7 and 8 in place thereof:

3.(Amended) A method according to claim 1 wherein the patient is exhibiting diabetes or is at risk from developing diabetes.

4.(Amended) A method according to claim 1 wherein the patient is treated with an antipsychotic agent.

7.(Amended) A method according to claim 4 wherein the dosage of the antipsychotic agent is decreased during treatment with an effective amount of quetiapine or a pharmaceutically acceptable salt thereof.

8.(Amended) A method according to claim 7 wherein the dosage of the antipsychotic agent is decreased to zero.

RESPONSE

Remarks concerning the amendment:

Applicants request that the amendment to the claims requested herein be entered before calculation of the filing fee.

The precise changes being made by the claim amendments are set forth in the amended claims presented in an Appendix hereto. In order to clearly show the changes, in the appendix all deleted material is show bracketed and lined through, thus: [~~deleted material~~]; and introduced material is shown underlined, thus: introduced material.

The undersigned certifies that the requested amendments introduce no new matter or any matter unsupported by the specification as originally filed.

The amendment removes multiply-dependent claims and after entry of the requested amendments four independent claims and 12 total claims are submitted for examination.

Respectfully Submitted

November 8, 2001

By _____

Kenneth F. Mitchell
Attorney for Applicant
Reg. No. 42,007
Telephone: 302/886-7466

APPENDIX

3.(Amended) A method according to claim 1 [~~or 2~~] wherein the patient is exhibiting diabetes or is at risk from developing diabetes.

4.(Amended) A method according to claim 1 [~~any one of claims 1 to 3~~] wherein the patient is treated with an [~~another~~] antipsychotic agent.

7.(Amended) A method according to claim 4[~~any one of claims 4 - 6~~] wherein the dosage of the [~~other~~] antipsychotic agent is decreased during treatment with an effective amount of quetiapine or a pharmaceutically acceptable salt thereof.

8.(Amended) A method according to claim 7 wherein the dosage of the [~~other~~] antipsychotic agent is decreased to zero.

METHOD OF TREATMENT

This invention relates to a method of treating the weight of patients and is particularly concerned with a method of treating the weight of patients suffering from psychoses.

Schizophrenia is a chronic and debilitating illness that affects approximately 1% of the population worldwide. For many years, conventional antipsychotic agents have been widely used to treat schizophrenia; however, they are associated with undesirable motor symptoms (extrapyramidal symptoms [EPS]) such as akathisia, dyskinesia, bradykinesia and parkinsonism, which are known to contribute to poor compliance with treatment. Such adverse effects of the older, typical antipsychotics caused a great deal of distress to patients but were tolerated as being inevitable in the treatment of psychotic symptoms. Even so, studies have suggested that 40% of patients stopped taking their medication within 1 year and 75% of patients stopped within 2 years (Perkins, 1999, J. Clinical Psychiatry 60 (suppl. 21), pp 25-30).

Many of the newer, atypical antipsychotic agents have an improved tolerability profile. With the resulting diminution in prevalence of the very debilitating EPS, more attention is being focused on other side effects of these agents, including a propensity to induce weight gain, seen with most atypical antipsychotics to a greater or lesser degree (Wirshing et al, 1999, J. Clinical Psychiatry 60: 358-63). In some cases, this may adversely affect patients' quality of life and possibly treatment compliance.

It has been recognized for more than 40 years that there is an association between antipsychotic medication and weight gain. In the past, weight gain has been linked to efficacy of antipsychotic medication, with research linking a positive outcome with increased weight. However, more recent research has shown this not to be the case (Umbricht et al, 1994, J. Clinical Psychiatry 55 (suppl. B): 157-60; Bustillo et al, 1996, American J. Psychiatry 153: 817-9).

Weight gain is associated with increased morbidity and mortality from a wide range of conditions including hypertension, coronary heart disease, cerebrovascular disease, type 2 diabetes mellitus, various cancers, sleep apnea and respiratory problems. It is also linked with morbidity related to the disease being treated itself. Studies have shown that the side effect of weight gain causes relatively more distress than many of the other common side effects associated with antipsychotic medication (Weiden, 1999). If weight gain is considered by the

patient to be unacceptable, compliance with the antipsychotic may be reduced and a worsening of the psychotic condition may ensue.

The extent to which each of these antipsychotic agents is associated with weight gain varies considerably (Allison et al, 1999, Am. J. Psychiatry 156: 1686-96; Wirsching et al, 1999). Weight gains of 3.99, 3.51 and 2.00 kg have been estimated following 10 weeks treatment with clozapine, olanzapine and risperidone, respectively (Allison et al, 1999).

Simansky et al, (Am. Psychiatry Association Meeting, Washington, USA, May, 1999) report on weight gains associated with treatment using ziprasidone, risperidone, quetiapine, olanzapine or clozapine. They confirm that the largest weight gains are associated with treatment using olanzapine or clozapine. They report that quetiapine is associated with a weight gain greater to that seen with risperidone and greater than that seen with ziprasidone. However, this report is based on an extrapolation to a ten week period based on an estimate at week 6 of treatment.

We have unexpectedly found that quetiapine is associated with a small mean weight increase in the first 5-6 weeks of treatment with little further mean change observed over 12 months of treatment. Actual mean weight increase for quetiapine treated patients differs markedly from the extrapolated figures reported by Simansky et al.

According to the present invention, there is provided a method of treating the weight of a patient which comprises administering an effective amount of quetiapine or a pharmaceutically acceptable salt thereof to said patient.

In another aspect, the present invention provides quetiapine or a pharmaceutically acceptable salt thereof for use in treating the weight of a patient.

In yet a further aspect, the present invention provides the use of quetiapine or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating the weight of a patient.

Quetiapine is 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)-dibenzo[b,f][1.4]thiazepine. This compound pharmaceutically acceptable salts thereof and use in treating schizophrenia are described in granted European Patent No. EP 240,228.

In particular, the patient is suffering from psychoses.

It is well recognized that there is a link between obesity and diabetes, especially type II diabetes, and that moderate to severe obesity increases the risk of developing diabetes. It is also widely accepted that weight loss results in metabolic improvement and hence in glycaemic control and insulin sensitivity which in turn give rise to improvements in

cardiovascular risk factors. This is reported by, for example, Bosello et al, Int. J. of Obesity, (1997) 21, Suppl 1, S10-13.

Weight gain in patients is generally undesirable but is more so in patients who are diabetic or who are at risk from developing diabetes.

Accordingly, the present invention further provides a method of treating the weight of a patient who is exhibiting diabetes or is at risk from developing diabetes which method comprises administering an effective amount of quetiapine or a pharmaceutically acceptable salt thereof to said patient. In particular, the patient is suffering from psychoses.

In an alternative aspect of the present invention, there is also provided a method of treating psychoses in a patient who is diabetic or who is at risk from developing diabetes which method comprises administering an effective amount of quetiapine or a pharmaceutically acceptable salt thereof to said patient.

In particular the patient is diabetic, that is exhibiting one or more of the symptoms of diabetes.

Quetiapine and pharmaceutically acceptable salts thereof are particularly effective in inducing weight loss in patients who have tended to gain weight when treated with other antipsychotics such as clozapine or olanzapine, in particular clozapine. Under such circumstances, quetiapine or pharmaceutically acceptable salts thereof may reverse at least part of any weight gained as a result of treatment with the antipsychotic such as clozapine or olanzapine, in particular clozapine.

In a particular aspect, the dosage of the other antipsychotic agent, such as clozapine or olanzapine, is decreased during treatment with quetiapine or pharmaceutically acceptable salt thereof.

The method of treatment of the present invention relates to short term (5-6 weeks), medium term (1-6 months) and long term (6 months-2 years or more) treatment, and is particularly valuable in medium term and long term treatment.

Quetiapine may be administered as the compound, 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)-dibenzo[b,f][1.4]thiazepine or may be administered in the form of a pharmaceutically acceptable salt. Examples of suitable salts include, for example, chloride, maleate, fumarate, citrate, phosphate, methane sulphonate and sulphate salts. Preferred salts include fumarates and a particularly preferred salt is the hemi-fumarate.

It is generally preferred that 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)-dibenzo[b,f][1.4]thiazepine is administered in the form of a pharmaceutically acceptable salt, and in particular a fumarate (2:1) salt.

In the treatment of the diseases and conditions mentioned above quetiapine or a pharmaceutically acceptable salt may be administered orally or parenterally in a conventional dosage form such as tablets, pills, capsules, injectables or the like. The dosage in mg/kg of body weight of the compound used to treat mammals will vary according to the size of the mammal and particularly with respect to the brain/body weight ratio. In general, a higher mg/kg dosage for a small animal such as a dog will have the same effect as a lower mg/kg dosage in an adult human. A minimum effective dosage for quetiapine or a pharmaceutically acceptable salt thereof will be at least about 1.0 mg/kg of body weight per day for mammals with a maximum dosage for a small mammal such as a dog, of about 200 mg/kg per day.

For humans, a dosage of about 1.0 to 40 mg/kg per day will generally be effective.

Typically, a dosage of about 25mg to 800mg per day will generally be effective. Usually, a dosage of about 150mg to 750mg per day will be administered, with a convenient dosage being about 300mg per day. In some groups of patients a lower dosage may be preferred such as 100mg per day. The dosage can be given once daily or in divided doses, for example, 2 to 4 doses daily. The dose may be conventionally formulated in an oral or parenteral dosage form by compounding 25 to 500 mg per unit dosage of conventional vehicle, excipient, binder, preservative, stabilizer, flavor or the like as called for by accepted pharmaceutical practice, for example, as described in US Patent 3,755,340.

Quetiapine or a pharmaceutically acceptable salt may be used in pharmaceutical compositions as the sole active ingredient or may be contained in a pharmaceutical composition together with one or more other active ingredients, or it may be co-administered with one or more known drugs.

Quetiapine or a pharmaceutically acceptable salt may be administered in conjunction with one or more other agents useful for treating diabetes.

Quetiapine or a pharmaceutically acceptable salt may be administered in conjunction with one or more other agents useful for treating psychoses.

As indicated above, where quetiapine or a pharmaceutically acceptable salt is administered in conjunction with another agent it may be administered simultaneously, sequentially or separately with that other agent or agents. Thus, as indicated above, quetiapine

or a pharmaceutically acceptable salt may be formulated with the other agent or agents or may be presented as a separate formulation.

Thus, in one aspect of the present invention, there is provided a pharmaceutical composition comprising quetiapine or a pharmaceutically acceptable salt and an agent known for treating diabetes together with a pharmaceutically acceptable diluent or carrier.

In a further aspect there is provided a pharmaceutical composition comprising quetiapine or a pharmaceutically acceptable salt and an agent for treating diabetes for simultaneous, sequential or separate administration.

The preparation of 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)-dibenzo[b,f][1.4]thiazepine and its pharmaceutically acceptable salts is described in, for example, granted European Patents Nos. EP 240,218; EP 282,236 and in International Patent Application No. PCT/GB98/02260. This compound is commercially available under the generic name quetiapine fumarate.

The invention will now be illustrated with reference to the following, non-limiting examples in which quetiapine was used as the fumarate (2:1) salt..

Example 1

Body weight data were collected for a group of 65 randomly-selected schizophrenic patients who were on clozapine initially (200 - 800 mg/day for 6 months) and then had quetiapine added to their therapy. Weights were recorded monthly, and status of diabetes follow-up was also performed. Clozapine dosages were reduced as quetiapine was added. The duration of treatment with quetiapine was 10 months. Data were extracted from retrospective chart review of 65 patients who were prospectively assigned to clozapine-quetiapine therapy. All 65 patients showed weight loss ranging from 0.5 to 23 lbs, with a mean loss of 3.98 lbs, after the first month of combination treatment; the quetiapine dose at one month ranged from 200 - 800 mg/day. The improvement continued throughout the 10-month study period. Total weight loss ranged from 1 to 41 lbs, with a mean loss of 9.2 lbs over the course of the study. Twenty per cent of patients developed diabetes during clozapine monotherapy and each showed significant improvement of diabetes with addition of quetiapine, as assessed through monthly blood monitoring and clinical improvement.

Thus, an unexpected clinical effect of quetiapine is its apparent propensity to induce weight loss and help with diabetes management in patients who gain weight and develop diabetes on clozapine.

Example 2

427 patients (277 male; 150 female) were treated with quetiapine monotherapy during controlled and open-label extension studies for up to 3.5 years and weight changes were monitored at specified time intervals throughout this period. The patients were in the age range 18-75 with a mean age of 37.3 years.

Patients were grouped using an observed cases approach within specified time intervals. Data on patients who received quetiapine monotherapy during the controlled portion of the trial and/or quetiapine during the open-label extension period are reported. Data were obtained for 30% of patients for at least one year.

Over the first 4 weeks, a mean weight loss of 0.36 Kg (n=17) was recorded. At subsequent time intervals weight changes were -0.17 kg (n=49) at weeks 5-8; +1.58 kg (n=171) at weeks 9-13; +0.29 kg(n=153) at weeks 14-26; +1.73 kg (n=128) at weeks 27-39; -1.47 kg (n=37) at weeks 40-52; +2.00 kg (n=116) at weeks 53-78; +3.43 kg (n=64) at weeks 79-104; +3.45 kg (n=44) at weeks 105-130 and +0.36 kg (n=9) at weeks 131-156. Patients received a mean quetiapine dosage of approximately 475 mg/day after one year of open-label treatment. Only one patient withdrew from the open-label study due to an adverse event of weight gain.

Thus, an unexpected clinical effect of quetiapine is its apparent capability of being associated with minimal weight gain unlike olanzapine and clozapine.

Example 3

The following illustrates representative pharmaceutical dosage forms containing the compound 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)-dibenzo[b,f][1,4]thiazepine fumarate (2:1).

(a) Tablet	mg/tablet
Quetiapine fumarate	50.0
Mannitol, USP.....	223.75
Croscarmellose sodium.....	6.0
Maize starch.....	15.0
Hydroxypropylmethylcellulose (HPMC),	2.25
Magnesium stearate.....	3.0

(b) Capsule

Quetiapine fumarate.....	10.0
Mannitol, USP.....	488.5
Croscarmellose sodium.....	15.0
Magnesium stearate.....	1.5

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

A preferred formulation is that available commercially as quetiapine fumarate.

CLAIMS

1. A method of treating the weight of a patient which comprises administering an effective amount of quetiapine or a pharmaceutically acceptable salt thereof to said patient.

2. A method according to claim 1 wherein the patient is suffering from psychoses.

3. A method according to claim 1 or 2 wherein the patient is exhibiting diabetes or is at risk from developing diabetes.

4. A method according to any one of claims 1 to 3 wherein the patient treated with another antipsychotic agent.

5. A method according to claim 4 wherein the antipsychotic agent is clozapine or olanzapine.

6. A method according to claim 5 wherein the antipsychotic agent is clozapine.

7. A method according to any one of claims 4 - 6 wherein the dosage of the other antipsychotic agent is decreased during treatment with an effective amount of quetiapine or a pharmaceutically acceptable salt thereof.

8. A method according to claim 7 wherein the dosage of the other antipsychotic agent is decreased to zero.

9. A method of inducing weight loss in a patient suffering from psychoses who has previously been treated with an antipsychotic agent which comprises administering an effective amount of quetiapine or a pharmaceutically acceptable salt thereof to said patient.

10. A method according to claim 9 wherein the antipsychotic agent was clozapine or olanzapine.

11. Quetiapine or a pharmaceutically acceptable salt thereof for use in treating the weight of a patient.

12. The use of quetiapine or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating the weight of a patient.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD OF TREATMENT

(57) Abstract: A method of treating weight in patients, in particular those suffering from psychoses, by administering the antipsychotic agent quetiapine.

WO 00/71106 A2

270538-IPUS

Docket. No. _____

DECLARATION (37 C.F.R. § 1.63) AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name, and

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

METHOD OF TREATING WEIGHT GAIN

the specification of which

☐ is attached hereto.

☐ was filed on as Application No. and was amended on .

x was filed on 16 May 2000 as PCT International Application No. PCT/GB00/01875 and was amended under PCT Article 19 on , if applicable.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with 37 C.F.R. § 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119, of any United States provisional applications or foreign application(s) for patent or inventor's certificate or of any PCT International Application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application for patent or inventor's certificate or any PCT International Application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application on which priority is claimed:

Application Serial No.	Country	Filing Date (Day/Month/Year)	Priority Claimed (Yes/No)
9911499.3	GB	19 May 1999	Yes
0002762.3	GB	8 February 2000	Yes

Docket. No. 70538-1

I hereby claim the benefit under Title 35, United States Code, Section 120, of any United States application(s) or PCT International Application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application(s) in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56, which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status (Patented, Pending, Abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint the attorneys associated with Customer Number 22466 to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and request that all correspondence about the application be addressed to the telephone number and address associated with Customer Number 22466.

Inventor's Signature Michael J Reinstein Date 10 30 01

Full name of sole or first inventor: Michael J. Reinstein
Residence Address: Chicago, US IL
Citizenship: US
Post Office Address: Forest Hospital/Rush Pres. Hospital, 4735 North Kenmore Street, Chicago, IL 60640, US

Inventor's Signature Andrew Martin Jones Date 23/10/01

Full name of second joint inventor: Andrew Martin Jones
Residence Address: Macclesfield, Great Britain GBN
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